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Synthesis of propargylamine derivatives of benzo[*d*]oxazole-2-thiol/oxazolo[4,5-*b*]pyridine-2-thiol as Antimicrobial agents

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Abstract:

A new series of propargylamine derivatives of mercaptobenzoxazole and oxazolo[4,5-*b*]pyridine-2-thiol derivatives **7a-7h** were synthesized and evaluated for their antimicrobial activity. The synthesis of propargylamine derivatives has been achieved by the sequential reaction of 2-aminophenol/2-aminopyridin-3-ol with CS_2, followed by alkylation and further reaction with secondary amines and formaldehyde undergoes a Mannich reaction at room temperature in the presence of CuI to afforded propargylamine derivatives. All the synthesized compounds were evaluated for their antimicrobial activity *viz. E. coli, P. Aeruginosa, S. Aureus* and *S.Pyogenus*and three pathogenic fungi *viz. C. Albicans, A. niger and A. Clavatus* and promising compounds were identified.

Keywords: Mannich bases**,** Propagylamine derivatives, Benzo[*d*]oxazole-2-thiol, oxazolo[4,5-*b*]pyridine-2-thiol,antibacterial activity, antifungal activity.

1. Introduction:

Multicomponent reactions are efficient and effective tool in organic synthesis for developing structurally diverse scaffold of biological interest due to their ability to form multiple bonds in a single step.[1] In particular, Mannich reaction is one of the identity of multicomponent reaction which consist with three component reaction of aldehyde, amines and compounds having an acidic C-H bonding which afford corresponding products, generally called Mannich bases.[2] Several compounds such as amines,[3] amides,[4] electron rich aromatic compounds[5] and terminal alkynes can serve as substrate in Mannich reactions. Mannich bases are found significant role in chemical and pharmaceutical industry.[6] Terminal alkyne in *Mannich* reaction gives the corresponding propargylamines, some of the propargylamines are known to exhibit biological activities, such as substituted 1-aryl-3-aminopropynes shows sedative, antiulceration, hypnotic, antispasmodic, analgesic and anti-inflammatory activities.[7]

Recently heterocyclic chemistry serve as key tool for the development of new bioactive molecules with wide range of pharmaceutical applications. In particular, benzene fused oxygen and nitrogen containing benzoxazoles and its derivatives display great devotion in the field of medicinal chemistry[8] due their significant biological properties such as melatonin receptor agonists,[9] COX inhibitor,[10] anticancer agents,[11] 55-HT_3 receptor antagonists[12] and HIV-1 reverse transcriptse inhibitors.[13] Interestingly, 2-mercaptobenzoxazole is a thiol derivative of benzoxazole moiety which exists in tautomeric forms of thiol and thione.[14] The extraordinary therapeutic properties of 2-mercaptobenzoxazole cause them as target compounds in organic synthesis and drug discovery.[15]

In trust of medicinal chemistry, the finding focused on synthesis of oxazolopyridine-2-thiol derivatives as it encompass pyridine moiety and might offer some advantages over 2-mercaptobenzoxazole moiety. The favourable properties of pyridine fragment like Water solubility, site for protonation and salt formation could enhance the interaction with targeted protein *via* hydrogen bonding and may help in modulating the physical and biological property of the molecule.

Therefore, it was projected that chemical entities with propargylamine with oxazolopyridine-2-thiol scaffold in one framework would result in improved biological activities. In view of these verdicts, we have attempted to synthesize propargylamine derivatives of mercapto benzoxazole and oxazolo[4,5-*b*]pyridine-2-thiol and evaluate its antimicrobial activity. Hence, here we disclose the synthesis of propargylamine derivative of mercaptobenzoxazole and oxazolo[4,5-*b*]pyridine-2-thiol scaffolds and their anti-microbial activity.

2. Experimental

Materials and methods

All chemicals and reagents were purchased from commercially available source and were used without further purification. Reactions were monitored by TLC, performed on silica gel glass plates containing 60 GF-254, and visualization on TLC was achieved by UV light or iodine indicator. Column chromatography was performed with

Merck 60–120 mesh silica gel. ^{1}H and ^{13}C spectra were recorded Bruker UXNMR/XWIN-NMR (300 MHz) instruments. Chemical shifts (δ) are reported in ppm down field from internal TMS standard. ESI spectra were recorded on Micro mass, Quattro LC using ESI^{+} software with capillary voltage 3.98 kV and ESI mode positive ion trap detector. Melting points were determined by an open capillary tube melting point apparatus and were uncorrected.

General procedures

***Preparation of benzooxazole/pyridine oxazole* (3)**

2-aminophenol/3-hydroxy-2-aminopyridine **1** (4.5 mmol), carbon disulphide **2** (4 ml) and potassium hydroxide (5.35 mmol) were taken in a 100ml round bottom flask and refluxed in 10ml of 95% ethanol for 7-8 hours. The reaction mixture was cooled to room temperature and concentrated. The 1M aqueous HCl solution was added to this concentrated reaction mixture. The product was filtered and washed with water (2 x 10 ml) and air dried. The dried product was recrystallized with ethanol.

Preparation of 2-(prop-2-ynylthio)benzo[d] oxazole/2-(prop-2-ynylthio)oxazolo[4,5-b] pyridine (5)

Benzo[*d*]oxazole-2-thiol/oxazolo[4,5-*b*]pyridine-2-thiol **3** (3.0 mmol) was dissolved in dry *N*,*N*-dimethylformamide (10 ml), and K_2CO_3 (6.0 mmol) was added and the reaction mixture was stirred for 25 min at room temperature. The propargyl bromide **4** (3.6 mmol) was added slowly drop wise to the above mixture over a period of 25 min and continued stirring for 4 h. after completion of reaction confirmed by TLC, The reaction was quenched with water and extracted with EtOAc (3 X 20 ml). The combined extracts were washed with water (3 X 25 ml) and brine (20 ml). The organic layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by silica gel chromatography (10 % ethyl acetate in hexane) gave the desired product.

Synthesis of Mannich* bases of *2-mercaptobenzoxazole/oxazole pyridine-2-thiaol derivatives (7a-h)

To a stirred solution of alkyne derivative **5** (1mmol) in tetrahydrofuran, 10 mol% CuI was added at room temperature. After stirring for 15 minutes, mixture of formaldehyde (1.5 equiv.) and secondary cyclic amine **6**(1mmol) were added and stirring was continued for 4–6 h at the same temperature. After completion of reaction as indicated by TLC, the reaction mixture was quenched by saturated NH_4Cl solution, diluted with water and extracted with ethyl acetate (2X15 ml).The combined organic layer was washed with brine solution, dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography using ethyl acetate/*n*-hexane gradients to afford Mannich base of 2-mercaptobenzoxazole/oxazole pyridine-2-thiaol derivatives **7a-h** as a pure product.

2-((4-morpholinobut-2-yn-1-yl)thio)benzo[d] oxazole (7a)

Yield 70%, m.p. 70-73^{0}C, IR (KBr): ν_{max} cm^{-1} 2934, 2101, 1641, 1560, 1259, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.47 – 2.52 (m, 4H), 3.31 (s, 2H), 3.67 – 3.72 (m, 6H), 7.40 – 7.48 (m, 2H), 7.60 – 7.69 (m, 2H), ^{13}C NMR(75 MHz, $CDCl_3$): δ 22.98, 47.33, 51.86, 66.61, 79.96, 81.47, 109.00, 120.63, 123.78, 124.44, 141.50, MS for $C_{15}H_{16}N_2O_2S$ (ESI): *m/z* 289 $[M+H]^{+}$.

2-((4-(piperidin-1-yl)but-2-yn-1-yl)thio)benzo[d] oxazole (7b)

Yield 63%, m.p.78-80^{0}C, IR (KBr): ν_{max} cm^{-1} 2930, 2103, 1645, 1563, 1262, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 – 1.67 (m, 5H), 2.30 – 2.57 (m, 5H), 3.27 (s, 2H), 3.55 (s, 2H), 6.89 – 7.00 (m, 2H), 7.24 – 7.40 (m, 2H), ^{13}C NMR(75 MHz, $CDCl_3$): δ 22.54, 23.67, 25.68, 47.74, 53.28, 79.31, 82.08, 110.28, 120.63, 123.70, 124.43, 141.42, 150.11, MS for $C_{16}H_{18}N_2OS$ (ESI): *m/z* 286 $[M+H]^{+}$.

2-((4-(piperazin-1-yl)but-2-yn-1-yl)thio)benzo[d] oxazole (7c)

Yield 74%, m.p. 72-75^{0}C, IR (KBr): ν_{max} cm^{-1} 3258, 2960, 2116, 1659, 1514, 1249, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.40 – 2.58 (m, 4H), 2.67 – 2.98 (m, 4H), 3.12 (s, 2H), 3.29 (s, 2H), 4.46 (s, 1H), 7.33 – 7.42 (m, 2H), 7.55 – 7.68 (m, 2H), ^{13}C NMR(75 MHz, $CDCl_3$): δ 22.85, 47.17, 50.41, 52.23, 79.90, 82.30, 110.40, 120.92, 123.82, 126.07, 141.60, 150.41, MS for $C_{15}H_{17}N_3OS$ (ESI): *m/z* 288 $[M+H]^{+}$.

N-(4-(benzo[d]oxazol-2-ylthio)but-2-yn-1-yl)-N-phenylaniline (7d)

Yield 80%, m.p.90-92^{0}C, IR (KBr): ν_{max} cm^{-1} 2981, 2119, 1721, 1513, 1273, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (s, 2H), 4.79 (s, 2H), 6.69 – 6.88 (m, 8H), 7.08 – 7.15 (m, 2H), 7.30 – 7.45 (m, 2H), 7.56 – 7.69 (m, 2H), ^{13}C NMR(75 MHz, $CDCl_3$): δ 22.93, 46.92, 79.95, 81.95, 110.30, 117.80, 121.35, 123.71, 124.43, 128.85, MS for $C_{23}H_{18}N_2OS$ (ESI): *m/z* 371 $[M+H]^{+}$.

2-((4-morpholinobut-2-yn-1-yl)thio)oxazolo[4,5-b] pyridine (7e)

Yield 72%, m.p. 78-80^{0}C, IR (KBr): ν_{max} cm^{-1} 2930, 2107, 1669, 1511, 1244, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.50 – 2.64 (m, 4H), 3.40 (s, 2H), 3.61 – 3.73 (m, 6H), 7.25 – 7.32 (m, 1H), 7.44 – 7.53 (m,

1H), 8.15 – 8.24 (m, 1H), ^{13}C NMR(75 MHz, $CDCl_3$): δ 23.75, 48.65, 52.22, 66.85, 80.27, 81.84, 119.45, 121.37, 148.53, 150.30, 156.31, MS for $C_{14}H_{15}N_3O_2S$ (ESI): *m/z* 290 $[M+H]^+$.

2-((4-(piperidin-1-yl)but-2-yn-1-yl)thio)oxazolo [4,5-b]pyridine (7f)

Yield 68%, m.p. 109-111^{0}C, IR (KBr): ν_{max} cm^{-1} 2930, 2106, 1640, 1561, 1260, ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 – 1.76 (m, 5H), 2.35 – 2.58 (m, 5H), 3.28 (s, 2H), 3.56 (s, 2H), 7.26 – 7.33 (m, 1H), 7.45 – 7.53 (m, 1H), 8.17 – 8.26 (m, 1H), ^{13}C NMR(75 MHz, $CDCl_3$): δ 22.68, 23.81, 25.82, 47.88, 53.42, 79.45, 82.93, 120.77, 121.49, 148.43, 150.45, 156.46, MS for $C_{15}H_{17}N_3OS$ (ESI): *m/z* 288 $[M+H]^+$.

2-((4-(piperazin-1-yl)but-2-yn-1-yl)thio)oxazolo [4,5-b]pyridine (7g)

Yield 78%, m.p. 106-108^{0}C, IR (KBr): ν_{max} cm^{-1} 3269, 2920, 2106, 1664, 1511, 1296, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.62 – 2.74 (m, 4H), 2.84 – 2.89 (m, 4H), 3.16 (s, 2H), 3.31 (s, 2H), 4.40 (s, 1H), 7.24 – 7.31 (m, 1H), 7.43 – 7.54 (m, 1H), 8.16 – 8.24 (m, 1H), ^{13}C NMR(75 MHz, $CDCl_3$): δ 23.07, 47.18,50.42, 52.25, 79.92, 82.31, 120.93, 121.49, 148.76, 150.24, 156.40, MS for $C_{14}H_{16}N_4OS$ (ESI): *m/z* 289 $[M+H]^+$.

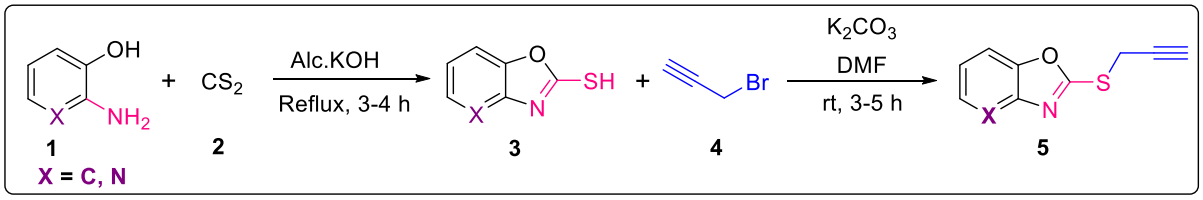
N-(4-(oxazolo[4,5-b]pyridin-2-ylthio)but-2-yn-1-yl)-N-phenylaniline (7h)

Yield 81%, m.p. 103-105^{0}C, IR (KBr): ν_{max} cm^{-1} 2934, 2117, 1592, 1440, 1236, ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (s, 2H), 4.80 (s, 2H), 6.70 – 6.89 (m, 8H), 7.09 – 7.20 (m, 2H), 7.25 -7.32 (m, 1H), 7.42 - 7.51 (m, 1H), 8.18 – 8.23 (m, 1H), ^{13}C NMR(75 MHz, $CDCl_3$): δ 23.13, 46.84, 80.22, 81.49, 120.57, 121.32, 123.70, 128.83, 137.43, 147.64, 156.33, MS for $C_{22}H_{17}N_3OS$ (ESI): *m/z* 372 $[M+H]^+$.

3. Results and discussion

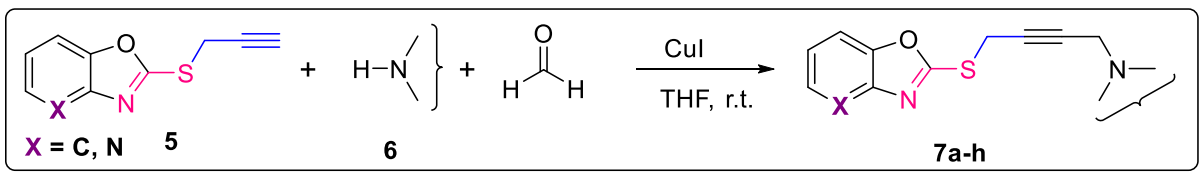
3.1. Chemistry

All the present propargylamine derivatives of mercaptobenzoxazole and oxazolo[4,5-b]pyridine-2-thiol derivatives were synthesized through sequential reactions as presented in scheme 1 and scheme 2. Initially, we synthesized compounds benzo[*d*]oxazole-2-thiol/oxazolo[4,5-*b*]pyridine-2-thiol **3** through reactions of 2-aminophenol/2-aminopyridin-3-ol **1** with carbondisulphide **2** using potassium hydroxide in water under reflux condition, affording the respective product in good yield (Scheme 1).[16,17] The structure of compound **3** was confirmed on the basis of Mass spectrometry. It shows *m/z* value at 152 $[M+H]^+$ for benzoxazole-2-thiol and *m/z* 153 $[M+H]^+$ for oxazolopyridine-2-thiol.



Scheme 1. Synthesis of propargyllated benzoxazole/pyridinoxazole.

Further compound **3** on reaction with propargyl bromide using two equivalent of inorganic base potassium carbonate in *N*,*N*-dimethyl formamide at ambient temperature resulted in the formation of 2-(prop-2-ynylthio)oxazolo[4,5-*b*]pyridine/2-(prop-2-ynylthio)benzo[*d*]oxazole **5**. The propargylated compound of benzoxazole-2-thiol and oxazolo pyridine-2-thiol were confirmed by ^{1}H NMR spectroscopy which shows signal at 4.09 and 4.17 ppm for two proton of CH_2 which consistent with compound **5**. Further multicomponent coupling reactions of alkyne compound **5,** formaldehyde and various secondary amines in the presence of CuI (10 mol%) in THF afford respective propargylamine derivatives **7a-h** (Scheme 2).[18] The results are summarized in Table 1.

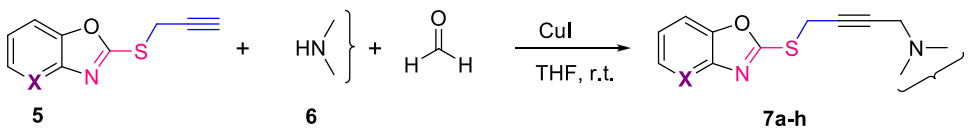


Scheme 2. Synthesis of propargylaminederivatives of 2-mercaptobenzoxazole/oxazolopridine-2-thiol.

All the propargylamine derivatives of mercaptobenzoxazole and oxazolo[4,5-b]pyridine-2-thiol derivatives were characterized by ^{1}H and ^{13}C NMR spectroscopy which show carbon carbon triple bond formation at 79 and 82 ppm in the ^{13}C NMR.

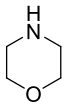
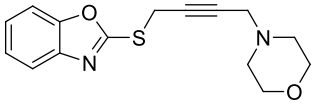
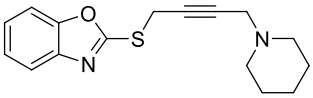
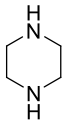
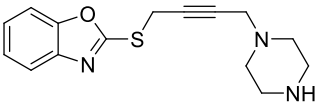
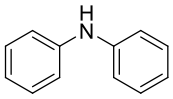
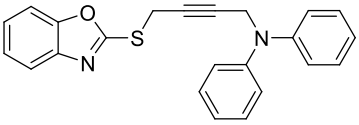
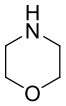
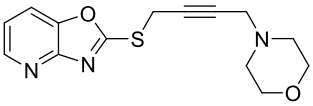
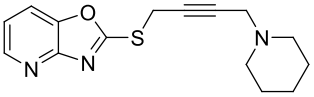
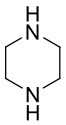
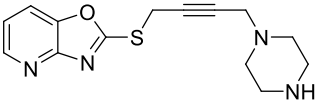
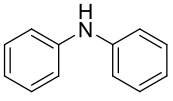
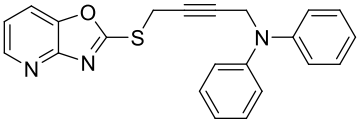
All the synthesized propargylamine derivatives of mercaptobenzoxazole and oxazolo[4,5-b]pyridine-2-thiol derivatives were evaluated for their antimicrobial activities.

Table 1. Mannich bases of 2-mercaptobenzoxazole/oxazole pyridine-2-thiaol.



5 6 7a-h

X = C, N

S.No.	HN	X	Product	Yield (%)
7a		C		70
7b		C		60
7c		C		62
7d		C		57
7e		N		61
7f		N		72
7g		N		63
7h		N		64

3.2 Biological Activity

3.2.1. Antimicrobial activity

The compounds **7a-h** were screened for their antibacterial activity against *E. coli, P. aeruginosa, S. aureus* and S. *pyogenus and* antifungal activity against *C. albicans, A. niger*and *A. clavatus*by Broth Dilution Method at different concentrations using DMSO as solvent. The serial dilution was prepared in primary and secondary screening. In primary screening 1000 micro/ml, 500 micro/ml, and 250 micro/ml concentrations of the synthesized drugs were taken. The synthesized drugs which were found active in this primary screening were further examined in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted for secondary screening to obtain 200 micro/ml 100 micro/ml, 50 micro/ml, 25 micro/ml, 12.5 micro/ml, and 6.250 micro/ml concentrations. The control tube was instantly sub cultured [before inoculation] which does not contains antibiotic by spreading a loopful uniformly over a quarter of plate of medium appropriate for the development of the test organism and put for incubation at 37 ^{0}C overnight. The MIC of the control organism is read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism is recorded as the MIC. The zone of inhibition of the growth was measured. The activity was compared with the standard drugs. A commercial antibacterial Ampiciline, Chloramphenicol, and antifungal Griseofulvin were also tested under similar conditions for comparison. The results are presented in Tables 2 and 3.

3.2.2. Antibacterial activity

The minimum inhibitory concentrations (MIC) of various synthetic compounds were screened against two representative gram-negative organisms, *viz. Escherichia coli* (MTCC443) and *Pseudomonas aeruginosa* (MTCC441) and gram-positive microorganisms, *viz. Staphylococcus aureus* (MTCC96) and *Streptococcus pyogenes* (MTCC442). The assays were performed by broth dilution techniques. Standard antibacterial agents such as ampiciline, chloramphenicol and ciprofloxin were also screened under similar conditions for comparison. The minimum inhibitory concentration (MIC) values are display in Table 2.

Table 2. Antibacterial activity of compounds **7a-7h**

Compound code	MIC (microgram/ml)			
	E. coli MTCC 443	*P. aeruginosa MTCC 441*	*S. aureus MTCC 96*	*S. pyogenus MTCC 442*
7a	200	100	500	500
7b	**100**	125	**200**	250
7c	**62.5**	100	**100**	250
7d	**62.5**	200	**100**	125
7e	200	250	**62.5**	**100**
7f	250	250	**200**	250
7g	200	200	250	200
7h	**62.5**	100	**125**	**100**
Ampiciline	100	--	250	100
Chloramphenicol	50	50	50	50

MIC values are given in (µg/ml) = Minimum inhibitory concentration, i.e. the lowest concentration of drug which completely inhibit bacterial growth

All compounds evaluated for their *in vitro* antibacterial activity. These results clearly indicate that compounds **7a–h** displayed significant activity with a high degree of variation against Ampiciline. Based on the results, 75% of the compounds showed considerable high activity against gram-positive *Staphylococcus aureus* (MTCC96) bacterial strains. 50% of the Compounds displayed significant activity against gram-negative *Escherichia coli*(MTCC443) bacterial strain and 25% of the compound showed good activity against gram positive *Streptococcus pyogenes (MTCC442)* while compounds are not showing sensitivity toward gram-negative *Pseudomonas aeruginosa* (MTCC441). Compounds **7b**, **7c**, **7d**, **7e**, **7f** and **7h** shows good activity against *Staphylococcus aureus* (MTCC96) than standard drug Ampiciline. Compound **7e** display highest activity against *S. aureus* than other compounds. Compound **7b**, **7c**, **7d**, and **7h** shows higher activity against gram-negative *E. coli* bacterial strains than standard compound Ampiciline, among these compounds, **7c**, **7d** and **7h** compounds are most active among the series against *E. coli*. Compounds **7e** and **7h** are only shows moderate activity against gram-positive *S. pyogenus*. Comparison with MIC value of tested

compound and standard drug, gram-positive bacterial strain show more sensitivity than gram-negative bacterial strains. Among the synthesized series, compounds **7c**, **7d**, **7e**, and **7h** are found to be most active candidates as antibacterial agents. However, considering the MIC values of the standard molecule, the order of sensitivity of these bacterial strain towards propargylamine derivatives of mercapto benzoxazole and oxazolo[4,5-b]pyridine-2-thiol derivatives is *S. aureus*>*E. coli*.>*S. pyogenus*>*P. aeruginosa.*

3.2.3. Antifungal activity

In vitro antifungal activity of the newly synthesized compounds were studied against the fungal strains, *Candida albicans* (MTCC 227), *Aspergillus niger (MTCC282)* and *Aspergillus clavatus (MTCC 1323)* using Greseofulvin as a standard antifungal drugs as shown in Table 3. The antifungal screening data of compounds **7a-h** revealed that compound **7b**, **7c**, and **7f** shows higher antifungal activity against *C. albicans*antifungal strain than Greseofulvin as standard drug, whereas compounds **7d**, **7g** and **7h** have equipotent activity with Greseofulvin standard drug against *C. albicans* antifungal strain. Compound **7b** only show similar activity with standard drug against *A. niger* antifungal strains. Among entire synthesized series compounds **7b**, **7c** and **7f** are found to be potent candidate as antifungal agents. Based on the results *C. albicans* strain displayed more sensitivity than other fungal strains with synthesized compounds. Considering the MIC values of the standard drug, the order of sensitivity of these fungal strain toward synthesized compound is C. *albicans*> A. niger>*A. clavatus*.

According to the structure–activity relationship studies, the propargylamine derivatives of pyridine-2-thiaol exhibited comparatively greater antimicrobial activity than 2-mercaptobenzoxazole derivatives. In particular, compounds with substituent morpholine, piperazine and diphenylamine displayed enhanced antimicrobial activity.

Table 3. Antifungal activity compound **7a-7h**

Compound code	MIC (microgram/ml)		
	C. albicans MTCC 227	*A. niger MTCC 282*	*A. clavatus MTCC 1323*
7a	1000	250	250
7b	**250**	**100**	>1000
7c	**250**	500	500
7d	500	1000	>1000
7e	1000	500	250
7f	**250**	500	500
7g	500	1000	1000
7h	500	1000	1000
Greseofulvin	500	100	100

MIC values are given in (µg/ml) = Minimum inhibitory concentration, i.e. the lowest concentration of drug which completely inhibit fungal growth

Conclusion

A series of propargylamine derivatives of mercaptobenzoxazole and oxazolo[4,5-b]pyridine-2-thiol derivatives have been synthesized and screened for their antimicrobial activity. The results of antibacterial screening reveal that compounds **7c**, **7d, 7e** and **7h** showed good inhibition toward bacteria strain with Ampiciline drug and compounds **7b, 7c,** and **7f** exhibited higher inhibition towards fungal strain with Greseofulvin drug. *S. aureus* antibacterial strain shows more sensitivity toward synthesized compound while in antifungal strain, *C. albicans*is found to be most sensitive.

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References:

[1] (a) Tietze, L. F., Beifus, U. (1993). Sequential Transformation in Organic Chemistry: A synthetic stategy with a futire. *Angew. Chem., Int. Ed., 32*, 131. (b) Tietze, L. F. (1996). Domino reaction in Organic synthesis. *Chem. Rev., 96*, 115. (c) Khan, A. T., Choudhury, L. H., Parvin, T., Ali, M. A. (2006). $CeCl_3 \cdot 7H_2O$: an efficient and reusable catalyst for the preparation of β-acetamido carbonyl compounds by multi-component reactions (MCRs). *Tetrahedron Lett.,47*, 8137. (d) Bonne, D., Coquerel, Y., Constantieux, T., Rodriguez, J. (2010). 1,3-Dicarbonyl compounds in stereoselectivedominoand multicomponent reactions. *Tetrahedron: Asymmetry, 21*, 1085. (e) Toure, B. B., Hall, D. G. (2009). Natural product synthesis using multicomponent reaction strategies. *Chem. Rev., 109*, 4439.

[2] (a) Tramonitini, M., Angiolini, L. (1994). Mannich-Bases, Chemistry and Uses, CRC: Boca Raton, FL. (b) Lehmann, F., Pilotti, A., Luthman, K. (2003). Efficient large scale microwave assisted Mannich reactions using substituted acetophenones. *Mol. Diversity, 7*, 145. (c) Hayashi, Y., Tsuboi, W., Ashimine, I., Urushima, T., Shoji, M., Sakai, K. (2003). The direct and enantioselective, one-pot, three-component, cross-Mannich reaction of aldehydes. *Angew. Chem., 115*, 3805-3808. (d) Padwa, A., Waterson, A. G., (2000). Studies dealing with Thionium ion promoted mannich cyclization reactions. *J. Org. Chem.65(1)*, 235-244. (e) Hwang, D. R., Uang, B. J. (2002). A modified mannich-type reaction catalyzed by VO(acac)(2). *J. Org. Lett., 4*, 463.

[3] Knapp, S., Hale, J. J., Bastos, M., Gibson, F. S. (1990). Amino protection using triazones. *Tetrahedron, 31*, 2109-2112.

[4] (a) Sharifi, A., Mohsenzadeh, F., Naimi-Jamal, M. R. (2000), Solvent free preparation of monoacylaminals assisted by microwave irradiation. *J. Chem. Res. 8*,394-396, (b) Hamlet, A. B., Durst, T. (1983). 1-(Dialkylaminomethyl)-azetidin-2-ones. Intermediates in a highly stereoselective preparation of trans-3,4-disubstituted azetidin-2-ones. *Can. J. Chem., 61(2)*, 411-415.

[5] (a) Mojtahedi, M. M., Sharifi, A., Mohsenzadeh, F., Saidi, M. R. (2000). Microwawe-assisted aminomethylationof electron-rich compounds under solvent-free condition. *Synt. Comm., 30*, 69-72; (b) Sharifi, A., Mirzaei, M., Naimi-Jamal, M. R. (2001). Solvent-free aminoalkylation of phenols and indoles assisted by microwave irradiation. *Monatsh Chem., 132(7)*, 875-880.

[6] (a) Karlen, B., Lindeke, B., Lindgren, S., Svensson, K. G., Dahlbom, R., Jenden, D. J., Giering, J. E. (1970). Acetylene compounds of potential pharmacological value. XIV. N-(tert-aminoalkynyl)-substituted succinimides and maleimides. Class of central anticholinergic agents. *J. Med. Chem., 13(4)*, 651-657., (b) Cook, S. C., Dax, S. L. (1996). Cyclic urea HIV protease inhibitors containing alkynyl- and alkenyl-tethered heterocycles in the P2 region. *Bioorg. Med. Chem. Lett., 6*, 797-802, (c) Dahlbom, R., Karlen, B., George, R., Jenden, D. J. (1966). Acetylene compounds of potential pharmacological value. 8. N-(4-dialkylamino-2-butynyl)-substituted cyclic imides. *J. Med. Chem., 9*, 843.

[7] AziendeChimicheRiuniteAngelini Francesco, British patent (1967). 1055548, CA 66:105003u.

[8] (a) Rodriguez, A. D., Ramirez, C., Rodriguez, I. I., Gonzales, E. (1999). Novel antimycobacterialBenzoxazole alkaloids, from the West Indian Sea whip *Pseudopterogorgiaelisabethae*. *Org. Lett., 1*, 527–530, (b) Kobayashi, J., Madono, T., Shigemori, H. (1995). Nakijinol, a novel sesquiterpenoid containing a benzoxazole ring from an Okinawan sponge. *Tetrahedron Lett.,36*, 5589–5590. (c) Huo, C., An, D., Wang, B., Zhao, Y., Lin, W. (2005). Structure elucidation and complete NMR spectral assignments of new benzoxazolinone glucoside from *Acanthus ilicifolicus.Magn. Reson. Chem., 43*, 343–345, (d) Rodriguez, I. I., Rodriguez, A. D. (2003). Homopseudopteroxazole, a new antimycobacterialditerpene alkaloid from *Pseudopterogorgiaelisabethae*. *J. Nat. Prod., 66*, 855–857, (e) Haansuu, J. P., Klika, K. D., Soderholm, P. P., Ovcharenko, V. V., Pihlaja, K., Haahtela, K. K., Vuorela, P. M. (2001). Isolation and biological activity of frankiamide. *J. Ind. Microbiol. Biotechnol.27*, 62–66.

[9] Sun, L. Q., Chen, J., Bruce, M., Deskus, J. A., Epperson, J. R., Takaki, K., Johnson, G., Iben, L., Mahle, C. D., Ryan, E., Xu, C. (2004). Synthesis and structure-activity relationship of novel benzoxazole derivatives as melatonin receptor agonists. *Bioorg. Med. Chem. Lett.14*, 3799–3802.

[10] Paramshivappa, R., Kumar, P. P., Subba Rao, P. V., Srinivase Rao, A. (2003). Design, synthesis and biological evaluation of benzimidazole/benzothiazole and benzoxazole derivatives as cyclooxygenase inhibitors. *Bioorg. Med. Chem. Lett., 13*, 657–660.

[11] Kumar, D., Jacob, M. R., Reynolds, M. B., Kerwin, S. M. (2002). Synthesis and evaluation of anticancer benzoxazoles and benzimidazoles related to UK-1. *Bioorg. Med. Chem., 10*, 3997–4004.

[12] Lopez-Tudanca, P. L., Labeaga, L., Innerarity, A., Alonso-Cires, L., Tapia, I., Mosquera, R., Orjales, A. (2003). Synthesis and pharmacological characterization of a new benzoxazole derivative as a potent 5-HT3 receptor agonist. *Bioorg. Med. Chem., 11*, 2709–2714.

[13] (a) Olsen, D. B., Carroll, S. S., Culberson, J. C., Shafer, J. A., Kuo, L. C. (1994). Effect of template secondary structure on the inhibitionof HIV-1 reverse transcriptase by a pyridinone non-nucleoside inhibitor. *Nucl. Acids Res.*, *22*, 1437–1443, (b) Staszewski, S., Massari, F. E., Kober, A., Gohler, R., Durr, S., Anderson, K. W., Schneider, C. L., Waterbury, J. A., Bakshi, K. K., Taylor, V. I., Hildebrand, C. S., Kreisl, C., Hoffstedt, B., Schleif, W. A., von Breisen, H., Rubsamen-Waigmann, H., Calandra, G. B., Ryan, J. L., Stille, W., Emini, E. A., Byrnes, V. W. (1995). Combination therapy with Zidovudine prevents selection of human immunodeficiency virus type 1 variants expressing high-level resistance to L-697, 661, a nonnucleoside reverse transcriptase inhibitor. *J. Infect. Dis.*, *171*, 1159–1165.

[14] Susperregui, J., Bayle, M., Léger, J. M., Déléris, G. (1998). Synthesis, structure and trypanocidal activity of dibutyltin derivatives of 2-mercaptobenzoxazole and 5-chloro-2-mercaptobenzothiazole. *J. Organomett. Chem.*, *556*, 105-110.

[15] Kohli , P., Srivastava , S. D., Srivastava, S.K. (2007). Synthesis and biological activity of Mercatobenzoxazole based thiazolidinones and their arylidenes. *J. Chin. Chem. Soc.*, *54*, 1003-1010.

[16] Gollapalli, N. R., Tallapaneni S. K. T. P., Medipalli K. L. S., Martha S., Rama Rao N. (2015). Synthesis, characterization and antimicrobial evaluation of novel 2-cyclic amine benzoxazole derivatives. *World Journal of Pharmacy and Pharmaceutical Sciences*, *4*, 1082-1093.

[17] Haider, S., Alam, M. S., Hamid, H., Shafi, S., Dhulap, A., Hussain, F., Alam, P., Umar, S., Pasha, M.A.Q., Bano, S., Nazreen, S., Ali, Y., Kharbanda, C. (2014). Synthesis of novel 2-mercaptobenzoxazole based 1,2,3-triazole as inhibitors of proinflammatory cytokines and suppressors of COX-2 gene expression. *Eur. J. Med. Chem. 81*, 204-217.

[18] Dadmal, T., Appalanaidu, K., Kosurkar, U.B., Jagdeeshbabu, N., Kumbhare, R.M. (2014). One-pot synthesis of 2-imino-4-(trifluoromethyl)thiazolidin-4-ol derivatives in a three-component reaction: Application to structurally diverse scaffolds of biological interest through subsequent reactions. Eur. *J. Org. Chem.*, *12*, 2468-2479.